

SUPPLEMENTARY MATERIAL

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VISNÚ-1 Clinical Investigators

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Table S1. Treatment exposure in the safety population

Variable	FOLFOX plus bevacizumab (n=177)	FOLFOXIRI plus bevacizumab (n=170)
Duration of treatment (weeks)	32.0 (18.0–47.7)	32.1 (13.9–50.6)
Number of cycles ^a	14 (8–20)	12 (6–21)
Relative dose intensity ^b (%)		
5-Fluorouracil	86.3 (76.4, 93.3)	75.3 (59.3, 86.2)
Irinotecan	—	75.4 (60.0, 86.3)
Oxaliplatin	87.3 (79.0, 93.3)	79.6 (68.1, 88.3)
Bevacizumab	89.2 (81.6, 93.7)	84.7 (73.7, 92.4)
Treatment delay (any cycle)	147 (83.1%)	150 (88.2%)
Dose reduction (any cycle)	91 (51.4%)	107 (62.9%)
Treatment discontinued due to treatment-related TEAE	17 (9.6%)	24 (14.0%)

Data are median (IQR) or n (%).

Abbreviations: FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; TEAE, treatment-emergent adverse event.

Note: For patients undergoing surgery during the treatment period, the treatment information prior to the first surgery has been included. Leucovorin was administered using different protocols and so is not included.

^aCycle length = 2 weeks.^bRelative dose intensity defined as quotient between the administered dose and the theoretical dose expressed as a percentage.

Table S2. Progression-free survival in the intention-to-treat population

Variable	FOLFOX plus bevacizumab (n=177)	FOLFOXIRI plus bevacizumab (n=172)
Patients with progression-free survival event	129 (72.9%)	112 (65.1%)
Earliest contributing event		
Progression	116	97
Death	13	15
Censored patients	48 (27.1%)	60 (34.9%)
Median (95% CI), months	9.3 (8.5, 10.7)	12.4 (11.2, 14.0)
IQR	7.4–14.0	8.3–16.9
Event-free rates (95% CI), %		
0 months	100.0 (100.0–100.0)	100.0 (100.0–100.0)
6 months	82.6 (75.7–87.6)	82.5 (75.6–87.6)
12 months	29.0 (21.4–37.0)	52.4 (43.2–60.8)
18 months	12.1 (7.0–18.6)	23.4 (16.0–31.6)
24 months	3.5 (1.1–8.5)	15.2 (9.1–22.8)
30 months	1.2 (0.1–5.5)	7.6 (3.4–14.0)
36 months	–	5.2 (1.9–11.1)
42 months	–	3.5 (0.8–9.4)
48 months	–	3.5 (0.8–9.4)
54 months	–	3.5 (0.8–9.4)
Stratified analysis		
p value (Log-rank)		0.0006
Cox model	Hazard ratio (95% CI)	Cox model P value
FOLFOXIRI plus bevacizumab vs FOLFOX plus bevacizumab	0.64 (0.49–0.82)	0.0006

Data are n (%) unless otherwise stated.

Abbreviations: CI, confidence interval; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.

Table S3. Univariate analysis of prognostic factors for progression-free survival

Variable	Reference category	Coefficient	SE	P value	HR (95% CI)
Treatment arm	FOLFOXIRI + bevacizumab	-0.455	0.133	0.001	0.63 (0.49–0.82)
Surgery for primary tumor	Yes	-0.163	0.139	0.243	0.85 (0.65–1.12)
CEA	≤5	-0.032	0.253	0.898	0.97 (0.59–1.59)
CTC count	>20 CTC/7.5 mL/blood	0.518	0.178	0.004	1.68 (1.18–2.38)
RAS status	Mutated	0.468	0.132	0.000	1.60 (1.23–2.07)
PIK3CA status	Mutated	-0.149	0.206	0.470	0.86 (0.57–1.29)
BRAF status	Mutated	0.715	0.213	0.001	2.04 (1.35–3.10)
Age	<65	-0.045	0.137	0.741	0.96 (0.73–1.25)
Sex	Female	0.285	0.139	0.041	1.33 (1.01–1.75)
ECOG	1	0.541	0.134	0.000	1.72 (1.32–2.23)
Tumor location	Right	0.373	0.142	0.009	1.45 (1.10–1.92)
Site of metastases	Multiple sites	0.370	0.141	0.009	1.45 (1.10–1.91)
Presentation	Metachronous	-0.326	0.261	0.212	0.72 (0.43–1.20)
Prior treatment	No	0.245	0.286	0.392	1.28 (0.73–2.24)
Prior radiotherapy	No	-0.116	0.415	0.780	0.89 (0.40–2.01)
Number of metastatic sites	>1	0.362	0.138	0.009	1.44 (1.10–1.88)

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; SE, standard error.

Table S4. Multivariate analysis of prognostic factors for progression-free survival

Variable	Reference category	Coefficient	SE	P value	HR (95% CI)
Treatment arm	FOLFOXIRI + bevacizumab	-0.414	0.137	0.003	0.66 (0.51–0.87)
Surgery for primary tumor	Yes	-0.208	0.159	0.192	0.81 (0.59–1.11)
CEA	≤5	0.301	0.278	0.278	1.35 (0.78–2.33)
CTC count	>20 CTC/7.5 mL blood	0.569	0.191	0.003	1.77 (1.21–2.57)
RAS status	Mutated	0.635	0.146	0.000	1.89 (1.42–2.51)
PIK3CA status	Mutated	-0.303	0.221	0.169	0.74 (0.48–1.14)
BRAF status	Mutated	0.911	0.250	0.000	2.49 (1.52–4.06)
Age	<65	-0.005	0.147	0.971	0.99 (0.75–1.33)
Sex	Female	0.197	0.144	0.171	1.22 (0.92–1.62)
ECOG	1	0.334	0.141	0.017	1.40 (1.06–1.84)
Tumor location	Right	0.288	0.157	0.067	1.33 (0.98–1.82)
Site of metastases	Multiple sites	0.001	0.484	0.998	1.00 (0.39–2.58)
Presentation	Metachronous	-0.065	0.633	0.919	0.94 (0.27–3.24)
Prior treatment	No	0.668	0.696	0.337	1.95 (0.50–7.62)
Prior radiotherapy	No	-0.719	0.497	0.148	0.49 (0.18–1.29)
Number of metastatic sites	>1	0.395	0.476	0.407	1.48 (0.58–3.78)

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio; SE, standard error.

Table S5. Overall survival in the intention-to-treat population

Variable	FOLFOX plus bevacizumab (n=177)	FOLFOXIRI plus bevacizumab (n=172)
Patients with event (death)	149 (84.2%)	136 (79.1%)
Censored patients	28 (15.8%)	36 (20.9%)
Median (95% CI), months	17.6 (15.1–21.2)	22.3 (17.8–26.4)
IQR	11.2–34.1	12.0–38.04
Event-free rates (95% CI), %		
0 months	100.0 (100.0–100.0)	100.0 (100.0–100.0)
6 months	90.9 (85.6–94.3)	87.1 (81.1–91.3)
12 months	68.2 (60.8–74.5)	75.8 (68.6–81.5)
18 months	48.3 (40.7–55.4)	57.6 (49.7–64.7)
24 months	39.5 (32.3–46.7)	46.6 (38.8–53.9)
30 months	31.6 (24.8–38.7)	33.4 (26.3–40.7)
36 months	20.2 (14.4–26.8)	26.0 (19.4–33.0)
42 months	14.6 (9.5–20.6)	22.2 (15.9–29.1)
48 months	10.4 (5.9–16.4)	17.8 (12.0–24.5)
54 months	10.4 (5.9–16.4)	15.8 (10.3–22.5)
60 months	6.9 (2.2–15.4)	15.8 (10.3–22.5)
Stratified analysis		
p value (Log-rank)		0.1407
Cox model	Hazard ratio (95% CI)	Cox model P value
FOLFOXIRI plus bevacizumab vs FOLFOX plus bevacizumab	0.84 (0.66–1.06)	0.1411

Data are n (%) unless otherwise stated.

Abbreviations: CI, confidence interval; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.

Table S6. Safety summary in the safety population

	FOLFOX plus bevacizumab (n=177)	FOLFOXIRI plus bevacizumab (n=170)	P value
All-grade TEAE	177 (100.0)	170 (100.0)	–
All-grade TEAE treatment-related	173 (97.7)	167 (98.2)	1.000
Serious TEAE	64 (36.2)	83 (48.8)	0.0170
Serious TEAE treatment-related	38 (21.5)	60 (35.3)	0.0042
Grade ≥3 TEAE	133 (75.1)	145 (85.3)	0.0178
Grade ≥3 TEAE treatment-related	119 (67.2)	133 (78.2)	0.0216
Grade 5 TEAE	13 (7.3)	14 (8.2)	0.7568
Grade 5 TEAE treatment-related	6 (3.4)	8 (4.7)	–
Grade ≥3 TEAE of interest			
Asthenia	15 (8.5)	29 (17.1)	0.0163
Diarrhea	12 (6.8)	39 (22.9)	<0.0001
Neutropenia	46 (26.0)	59 (34.7)	0.0772
Febrile neutropenia	4 (2.3)	14 (8.2)	0.0121
Mucositis	7 (4.0)	15 (8.8)	0.0628
Sensory neuropathy ^a	40 (22.6)	32 (18.8)	0.3860
Hypertension	13 (7.3)	11 (6.5)	0.7484
Intestinal perforation	9 (5.1)	4 (2.4)	0.1804

Data are n (%).

Abbreviations: FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; TEAE, treatment-emergent adverse event.

^aGrouped term which includes dysesthesia and paresthesia.

Table S7. Treatment-emergent adverse events in the safety population

	FOLFOX plus bevacizumab (n=177)		FOLFOXIRI plus bevacizumab (n=170)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Neutropenia	42 (23.7)	46 (26.0)	45 (26.5)	59 (34.7)
Diarrhea	71 (40.1)	12 (6.8)	91 (53.5)	39 (22.9)
Sensory neuropathy ^a	116 (65.5)	40 (22.6)	103 (58.2)	32 (18.8)
Asthenia	104 (58.8)	15 (8.5)	98 (57.7)	29 (17.1)
Mucositis	56 (31.6)	7 (4.0)	68 (40.0)	15 (8.8)
Febrile neutropenia	NA	4 (2.3)	NA	14 (8.2)
Vomiting	36 (20.3)	5 (2.8)	65 (38.2)	14 (8.2)
Thrombocytopenia	53 (29.9)	7 (4.0)	40 (23.5)	11 (6.5)
Hypertension	21 (11.9)	13 (7.3)	18 (10.6)	11 (6.5)
Anemia	36 (20.3)	5 (2.8)	37 (21.8)	8 (4.7)
Intestinal obstruction	0 (0)	1 (0.6)	1 (0.6)	7 (4.7)
Diminished appetite	42 (23.7)	2 (1.3)	51 (30.0)	5 (2.9)
Nausea	65 (36.7)	0 (0)	84 (49.4)	5 (2.9)
Abdominal pain	24 (13.6)	4 (2.3)	42 (24.7)	5 (2.9)
Hyponatremia	0 (0)	0 (0)	1 (0.6)	4 (2.4)
Intestinal perforation	0 (0)	5 (2.8) ^b	0 (0)	1 (0.6) ^b

Data are n (%). Events listed are grade 3/4 events that occurred in at least 2% of patients in either treatment group.

Abbreviations: FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; NA, not applicable.

^aGrouped term which includes dysesthesia and paresthesia.

^bIn addition, 4 (2.3%) patients in the FOLFOX-bevacizumab group, and 3 (1.8%) patients in the FOLFOXIRI-bevacizumab group had grade 5 intestinal perforation.

Table S8. Second-line and later anti-cancer treatments

	FOLFOX plus bevacizumab (n=177)	FOLFOXIRI plus bevacizumab (n=172)
Lines of therapy administered		
Second-line	130 (73.4)	118 (68.6)
Third-line	70 (39.5)	72 (41.9)
Fourth-line or later	26 (14.7)	34 (19.8)
Anti-cancer medications		
Fluoropyrimidines ^a	122 (68.9)	90 (52.3)
Irinotecan	114 (64.4)	84 (48.8)
Oxaliplatin	28 (15.8)	43 (25.0)
Trifluridine/tipiracil (TAS 102)	12 (6.8)	22 (12.8)
Anti-EGFR agents ^b	45 (25.4)	50 (29.1)
Cetuximab	34 (19.2)	30 (17.4)
Panitumumab	15 (8.5)	26 (15.1)
Anti-angiogenic agents ^b	89 (50.3)	83 (48.3)
Aflibercept	36 (20.3)	9 (5.2)
Bevacizumab	50 (28.3)	51 (29.7)
Regorafenib	17 (9.6)	33 (19.2)
Other	15 (8.5)	27 (15.7)

Data are n (%).

^aIncluded 5-fluorouracil and capecitabine.^bPatients may have received more than 1 agent.

Abbreviations: EGFR, epidermal growth factor receptor; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan.